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09/581,976	06/20/00	DALEMANS W	B45124

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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/581,976	DALEMANS ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *January 08, 01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) *1-11, and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) *1-11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *9727262.9* .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Amendment

The preliminary amendment filed on June 20, 2000 is acknowledged, since the claim 12 is canceled and Claim 16 has been added. Claims 1-11 and 13-16 are pending before the examiner.

Specification

The disclosure is objected to because of the following informalities:

(1). The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

(2). The language used in the specification is not conventional American English language, such as "tumour" and "immunise". Applicants are required to carefully review the disclosure of the specification and appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-11, 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8-10 and 15 are vague and indefinite in that the metes and bonds of the CpG oligonucleotide are not defined. The claims are interpreted in light of the specification, however since there are variety of CpG oligonucleotide in the art, the claims should point out which CpG oligonucleotide is intended in the said claims. This effects the dependent claims.

Claims 1 and 15 are further rejected in that the metes and bonds of the recitation of fusion partner are not defined. The claims are interpreted in light of the specification, however since there are many different kinds of protein that can be used as fusion partner, the claims should point out which fusion protein is intended in the said claims.

The term "optionally linked to" in claims 1and 15 is an open language which can not define what exactly do the said products consist of. The specification does not provide a standard for ascertaining in which situation that the E6 or E7 or E6/E7 should be linked or should not be linked to the fusion partners and an immunomodulatory CpG oligonucleotide. Therefor, the claims are considered in definite.

Claim 2 is vague and indefinite in that the metes and bonds of the "fragment thereof" are not defined. The claims are interpreted in light of the specification, the claims should point out what the exact size of the "fragment thereof" for teach fusion partner is referred in the said claim.

The term "derived" in claim 1 is a relative term, which renders the claim indefinite. The term "derived" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant case, the definition of derivation has many meaning, therefore, the claim is considered as indefinite.

Claims 4 and 5 are vague and indefinite in that the mutation are not defined. The claims are interpreted in light of the specification, however since there are different types of mutation in the art and different mutation render different results. The claims should point out what type of mutation is intended and further where does the mutation occur in E6 and E7 genes.

Claims 7 and 16 are vague and indefinite in that metes and bonds of the "additional HPV antigen" are not defined. The claims are interpreted in light of the specification, but the specification is rather deficient for teaching what the additional HPV antigen is referred in the said claims. Is the L1 or L2 of HPV antigen intended? Moreover, the recitation of "comprising" used in the claims is an open language which can not further defined what is the exact other antigen in the said plasmid. Since HPV genome encodes several antigen products, the claims should point out which other antigen is intended in the said claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a variety of composition comprising E6 or E7 protein or E6/E7 fusion protein of HPV16 or HPV18 that is linked to the fusion

partners plus an immunomodulatory oligodexynulceotide adjuvant that consists of CpG motif, wherein the said fusion partners consist of the protein D (Ser 20-Thr 127) of Heamophilius influenza B and the non-structural protein 1 (NS1) (4-81) of Influenza virus as well as a histidine residue or the bacterial Lyta motif of Strptococcus pneumonia (residue 188-305) and the NS1 (4-81) plus a histidine residue, and resulting in an enhanced Cytotoxic T cell Lysis (CTL) activity against E7/HPV16 antigen and partial tumor regression by co-administration of one construct (TCA308) consisting of E7 /HPV16 fused with protein D, NS1 sequence and histidine residues and an immunomodulatory CpG oligonucleotide (1826) into an E7 expressing tumor mouse model to produce an immune response, does not reasonably provide enablement for E6 or E7 optionally linked with all kinds of fusion partner plus additional antigen for induction of a preventive immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the instant case, the specification discloses several compositions made from E6 or E7 or E6/E7 fusion protein of HPV16 of HPV18 linked with some fusion partners as described above [Prot-D1/3-E7-His/HPV16 (TCA308), Prot-D1/3-E6-His/HPV16 (TCA307), fusion Protein-D1/3-E6/E7-His/HPV16 (TCA311), clyta-E7-His/HPV16 (TCA330), clyta-E6-His/HPV16 (TCA332), clyta-E6/E7-His/HPV16 (TCA331), Prot-D1/3-E7-His/HPV18 TCA313), Prot-D1/3-E6-His/HPV18 (TCA314), Prot-D1/3-E7-His/HPV18 (TCA328)], wherein the E7 can be made by two point mutation as Prot-D1/3-E7matated (cys24→Gly, Glu26→Gln)-His/HPV16 (TCA347) or Prot-D1/3-E7matated (cys27→Gly, Glu29→Gln)-His/HPV18 (TCA355). But the specification only present that one composition comprising construct TCA308 in combination with an immunomodulatory oligonucleotide CpG No. 2 (1826) injected into the E7 expressing tumor mouse models, can result in an enhanced activity of Cytotoxic T Lymphocyte (CTL) against E7 antigen of HPV16, partial tumor regression and a weak antibody response.

It is known in the art that the E7 or E6 is not a strong antigen, it usually get a weak immune response by itself without the combination with other HPV antigen(s).

In fact, the present invention of utilization of the composition TCA308 read only on some tumor regression by means of the increased CTL activity, but neither prevention nor completely treatment of the tumor induced by HPV has been taught. The specification is rather deficient for teaching that immunization of composition TCA 308 plus CpG oligonucleotide 1826 or any other composition with all kind of fusion partners can prevent the host animal from getting any HPV infection or tumor development by further challenging the animals with HPV after the immunization.

Moreover, the applicants are also remaindered that the field is unpredictable in that not every CpG motif can have such immunistimulating activity as evidenced by Yamamoto et al. (Immunobiology of Bacterial CpG-DNA, pp. 26-27, see the section 3.1 and 3.2). He teaches that although the hexamer palindromic sequences having -CG- motif are essential for inference (IFN) production and Nature Killer cell (NK) augmentation, some exceptional cases still exist. For instance, GTCGTT and GACGTT are active, and GACGTC is inactive (pp. 30, 2nd paragraph). It is also true that formula, purine purine cytosin quanine pyrimidine pyromidine (Pu-Pu-CG-Py-Py), which has been used wildly by many investigations, has many exceptions (pp. 31, 2nd paragraph). Even in the present case, the specification only shows that 1 out of 3 such oligonucleotide exhibits some augmentation of the CTL activity against the E7/HPV16 antigen and partial tumor regression.

Still further, the breadth and scope of claims read on vaccine, because to enable the invention a sustained immune response and a completely prevention of HPV induced tumor development would be required. Applicants are reminded that the field of such therapeutic vaccine is highly unpredictable. Therefore, the disclosed results can not be extrapolated to the long-term protection against HPV infection.

Especially considering the general and broad statements in the claims. With regard to an unpredictable field, this does not constitute an adequate disclosure. See Fiers v. Revel (25USPQ2d 1601 at 1606; and also decision by the Federal Circuit with regard to the enablement issues see Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001-1007). For example, the CAFC stated that "It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute enablement." (See page 1005 of the decision). This means that the disclosure

must adequately guide the art worker to determine, without undue experimentation. The applicant can not rely on the knowledge of those skilled in the art to enable the claims without providing adequate teaching.

In addition, the specification is rather deficient for teaching what the additional HPV antigen is, how it is inserted into the construct and what the behavior of the additional antigen is. Therefore, a person skill in the art would be required to do an undue experimentation to enable the full scope of the claimed invention.

As there is no clear teaching how the said compositions can induce a long-term immunity against any or all types of HPV infection and prevent the HPV induced tumor development, the lack of guidance for proper selection of the CpG oligonucleotide sequence which can enhance the immunity against any or all kinds of antigen from any types of the HPV, one of a skilled person in the art would be required to conduct large quantity of experimentation to enable the full scope of the claimed invention.

Therefore, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim. Many of these factors have been summarized *In re Wands, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988)*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim1-11 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boursenell et al. (Vaccine 1996, Vol. 14, pp. 1485-1494), Borysiewicz et al. (The Lancet 1996, Vol. 347, pp. 1523-1527), Edwards et al. (WO 96/19496), Carson et al. (WO 97/28259) and Chu et al. (J. Exp. Med. 1997, Vol. 186, pp. 1623-1631).

The present invention is drawn to the polynucleotide constructs which consist of the part of the coding sequence of E6 or E7 protein of E6/E7 fusion protein from HPV16

or HPV18 optionally linked to the fusion partner and a histidine residues, The administration of the E7 fused with protein D and NS1 protein with histadine tail (TCA308), in combination with an immunomodulatory CpG oligonucleotide (1826) as an adjuvant, results in an enhanced activity of CTL against E7 antigen and reduction of a E7 expressing tumor progress, wherein the E7 gene can also be modified by point mutation (cys24→gly, glu26→gln for E7 of HPV16 or cys27→gly, glu29→gln for E7 of HPV18) and fusion partners consisting of protein D of Haemophilius influenza B, non-structure protein NS1 from influenza virus as well as histadine residue or Lyta motif of Streptococcus pneumonia for the purification purpose.

Edwards et al. disclosed a vaccine composition consisting of E6 or E7 or E6/E7 fusion protein from HPV16 or E18, wherein the E6 or E7 or E6/E7 fusion protein can be a mutated variant that is able to elicit a humoral and /or cellular immune response against HPV antigen but has a less cell-transformation property (5, lines 1-29). In addition, the vaccine composition is also directed to optionally mixes with an adjuvant (pp.5, lines 6-8 and pp. 7, lines 6-11). Still further, Edwards et al. disclosed that the E6 and /orE7 moieties are optionally linked with some fusion protein, such as diphtheria etc. to enhance the immunogenecity and other fusion partner such as a glutathione-s-transferase (GST) moiety or histadine residue for the purification purpose (pp. 7, Lines 6-9). Edwards et al. did not teach where the point mutation of E7 can be made and he did not use immunomodulatory CpG motif oligonucleotide as an adjuvant. However, he taught a basis vaccine composition for using a vaccine comprising a construct of E6 or E7 or E6/E7 to immunize the host animal and eliciting a humoral and/or cellular immune response against E6 or E7 protein for the prevention or treatment of HPV infection and its related tumor.

Boursnell et al. further taught a vaccine composition made by modified fusion protein E6/E7 with two point mutations at cys24→gly and glu26→gln for E7/HPV16 or cys27→gly and glu29→gln for E7/HPV18. The said constructs possess much less neurovirulence and oncogenic potential. The injection of the said vaccine composition into a mice immunized with such composition (TP-HPV) can significantly induce an HPV-specific CTL activity correspondent to the HPV16 E7 antigen (see materials and

methods on pages 1486-1489 and results on pages 1489-1493). However, Boursnell et al. did not use the CpG oligonucleotide sequence as an adjuvant.

Still further to emphasis the state of the art, Applicants are referred to Borysiewicz et al wherein the art taught the utilization of the said composition in patients with late stage of cervical cancer developed an HPV-specific antibody and HPV-specific CTL . Once again this differs since they did not teach to use CpG oligonucleotide sequence as an adjuvant.

Chu et al. taught that synthetic oligonucleotides comprising CpG motif (one of them is nucleotide 1826) acts as an adjuvant that enhance the Th1-dominated response to co-administrated antigen (see entire document). Although Chu did not use the E6 or E7 as a co-administrated antigen, but she clearly demonstrated that the synthetic oligonucleotides containing CpG motif are potential adjuvants for human vaccine to elicit protective Th1 immunity.

Taken together, the above cited references are indicative of the state of the art as it applies to the entire invention. The one of ordinary skill in the art at the time of invention would have had access to the said references. The state of the art taught that the E6 or E7 of HPV16 and HPV18 has long been a well-characterized antigen known in the art for their property related to the cervical cancer development. The E7 antigen in combination with other HPV antigen have long been recognized and used as the target for developing CTL activity of Th1 type cellular immunity against E7 antigen in the art too. Some of the E6 or E7 fusion proteins have already been put into the clinical trials as evidenced by Borysiewicz et al. So does the adjuvant consisting of immunomodulatory oligonucleotide CpG motif (or called immunostimulatory sequences ISS) in vaccine composition as disclosed by Carson et al. Therefore, it is concluded that it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be amply motivated by the recited references to combine the method taught by Edwards et al. and Boursnell et al. and in view of Chu et al. and Carson et al. to combine the early disclosed HPV protein(s) along with a well known adjuvant such as CpG motif to induce an enhanced CTL activity against papillomavirus absent any unpredicted results. Hence the claimed invention as a whole is considered to be prima facie obvious absence unexpected results.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Boa Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:30 Am to 5:00 Pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li

January 17, 2001

ALI R. SALIMI
PRIMARY EXAMINER